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The role of vagal-neuroimmunomodulation index in patients with pulmonary arterial hypertension

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ABSTRACT

Aim: The vagal neuroimmunomodulation (NIM) index is reflective of the cholinergic inflammatory tone in many clinical circumstances as well as in healthy individuals. We aimed to investigate the relationship of NIM-index on the clinical course patients with PAH.

Material and Method: A total of 31 patients diagnosed with pulmonary arterial hypertension (PAH) were included in this study. Data on electrocardiography (ECG) and C-reactive protein (CRP) were retrospectively obtained from patients' electronic files retrospectively. The vagal NIM index was calculated as heart rate variability (HRV) to CRP ratio (HRV/CRP).

Results: During clinical follow-up, most patients required hospitalization at least once (21 vs. 10 patients). Consistent with the current literature and as expected, there was a significant difference between the groups in BNP values (394 ng/L vs 55 ng/L, p=0.005). HRV, CRP, and NIM-index values were not found to be significant between the groups.

Conclusion: NIM-index values were not associated with the need for hospitalization in patients with PAH.

Keywords: Heart rate variability, pulmonary arterial hypertension, C-reactive protein (CRP), neuroimmunomodulation

INTRODUCTION

Pulmonary arterial hypertension (PAH) is a rare disease that affects young people and women relatively more frequently (1). Idiopathic PAH (IPAH) is the most common type of PAH (1). Echocardiography (ECHO) provides the basic evaluation and right heart catheterization (RHC) ensures a definitive diagnosis. Therapeutic strategies can be summarized as specific PAH drugs, calcium channel blockers (CCBs) in responders, and finally lung transplantation.

Many clinical indicators and variables are used to predict the prognosis in patients with PAH (2). However, risk assessment in PAH patients remains unsatisfactory. Risk-stratification assessment needs to be further validated through outcome studies and optimized for patients with PAH.

The vagal-neuroimmunomodulation index (NIM-index), calculated as a ratio of vagally-mediated heart rate variability (vmHRV) and C-reactive protein (CRP), reflects the cholinergic activity and inflammatory status, and is associated with survival in the general population (3). In the current literature, no study addresses the relationship between the NIM-index and the prognosis of patients with PAH. Our aim in this study was to investigate the role of NIM-index in PAH patients.

MATERIAL AND METHOD

The study was carried out with the permission of Ankara City Hospital No:1 Clinical Researches Ethics Committee (Date: 07/09/2022, Decision No: E1-22-2807). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. With the ethics committee approval, the data were scanned retrospectively between 01.03.2019 and 01.07.2022.

A total of 196 patients were identified as pulmonary hypertension (PH). Of these, 32 patients in the pediatric age group (<18 years) were excluded. Of the remaining's, only 76 were in group 1 according to the Dana Point Classification of PH (4). After excluding patients whose heart rate variability (HRV) could not be calculated and whose ECG and C-reactive protein (CRP) values not available, finally 31 patients were included in the study.

HRV was calculated from baseline ECG at the time of diagnosis. For this purpose, root mean square of the successive differences (RMSSD) was used. Patients with atrial fibrillation (AF), extreme bradycardia/AV block and paced rhythm were excluded. CRP values were obtained from the local laboratory database. The baseline CRP values were recorded to coincide in terms

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of timing with ECGs. The NIM-index was calculated as a ratio of HRV (rMSSD) to CRP values (5). Finally, study patients was compared in terms of need for hospitalization (**Table 1**).

Table 1. Baseline demographic and clinical characteristics

	Hospitalization (-) n=10	Hospitalization (+) n=21	p value
Age (y), mean±SD	40.8±9.8	37.2±14.0	0.477
Sex (female), n (%)	5 (50.0)	15 (71.4)	0.244
CHF, n (%)	1 (10.0)	1 (4.8)	0.579
LVEF, %	60 [30-64]	60 [40-76]	0.696
sPAP (ECHO), mmHg	77.3±23.3	89.3±26.5	0.230
mPAP (RHC), mmHg	45.0±15.8	52.9±20.8	0.301
Laboratory			
NT-pro BNP (ng/L)	55 [39-887]	394 [43-11684]	0.006
Glucose (mg/dL)	90.60±10.11	92.38±21.09	0.803
Creatinine (mg/dL)	0.77±0.21	0.74±0.16	0.624
eGFR (ml/min/1.73m2)	107.90±16.63	109.95±18.03	0.756
WBC	6.29±1.40	7.35±2.73	0.164
HGB (g/dL)	14.71±3.51	15.50±3.88	0.592
HCT	44.62±11.23	48.48±12.32	0.409
PLT	238.6±67.4	214.6±124.5	0.574
NLR	2.51±1.04	2.94±1.61	0.381
vmHRV (RMSSD)	15.14 [7.75-43.59]	14.14 [0-116.19]	0.719
CRP (mg/L)	1.25 [0.5-23.4]	3.13 [0.5-162.3]	0.367
NIM-index	13.56 [0.82-34.64]	1.64 [0-232.38]	0.300
Drugs, n (%)			
ERAs	4 (40.0)	13 (61.9)	0.252
PDE5i	4 (40.0)	16 (76.2)	0.049
CCBs	2 (20.0)	0 (0)	0.034
PCA/PRA	1 (10.0)	9 (42.9)	0.067
sGCs	0 (0)	1 (4.8)	0.483

CHF: congestive heart failure; LVEF: left ventricular ejection fraction; sPAP: systolic pulmonary artery pressure; mPAP: mean pulmonary artery pressure; HRV: heart rate variability; NIM-index: the neuroimmunomodulation index; ERAs: endothelin receptor antagonists; PDE5i: phosphodiesterase 5 inhibitor; CCBs: calcium channel blockers; PCA: prostacyclin analogue; PRA: prostacyclin receptor agonist; sGCs: soluble guanylate cyclase stimulator.

Statistical analyses were performed with IBM SPSS Statistics software (ver. 25). The distribution of data was determined by Shapiro-Wilk test. Continuous variables were expressed as mean ± standard deviation or median (minimum-maximum) and categorical variables as frequency and percent. Categorical variables were compared using Pearson chi-square test. Continuous variables were compared with the independent sample t-test or the Mann-Whitney U test for two groups. The variables of age, gender, LVEF, sPAP, mPAP, glucose, creatinine, eGFR, NT-pro BNP, hemoglobin (HGB), hematocrit (HCT), neutrophil-lymphocyte ratio (NLR), CRP, HRV and NIM-index were used in Univariate Binary logistic regression analysis with the Enter method to determine risk factors according to the presence of hospitalization. p value of less than 0.05 was considered as statistically significant for all tests.

RESULTS

A total of 31 patients were included to final analyses. The mean follow-up period for the whole study population was 31±10 months. The patients were divided into 2 groups in terms of the need for hospitalization (**Table 1**). While ten patients were not hospitalized during the follow-up period, 21 patients were hospitalized at least once.

The groups were similar in terms of age and sex. Alike, there are no differences about presence of CHF and mean LVEF values. However, mean NT-pro BNP values were significantly higher in the hospitalization group (394 ng/L vs. 55 ng/L, p=0.006).

When the groups were compared in terms of PAH-specific drug therapy, only the use of PDE5i and CCBs was found to be different (p values are 0.049 and 0.034, respectively).

Both mean sPAP and mean mPAP values of patients were higher in the hospitalization group, but the difference was not statistically significant (**Table 1**).

There was no statistically significant difference between the groups in terms of HRV (14.14 vs 15.14, p=0.719) and CRP (3.13 vs. 1.25, p=0.367). Although the median NIM-index was found to be lower in the hospitalization group, this difference was not statistically significant (1.64 vs 13.56, p=0.300).

When univariate logistic regression analysis was performed, no variable was associated with hospitalization (**Table 2**).

Table 2. Univariate logistic regression analysis of the need for hospitalization

	Odds Ratio	CI (95%)	p value
Age	0.978	0.921-1.038	0.463
Sex	2.500	0.525-11.894	0.250
LVEF	1.034	0.937-1.142	0.503
sPAP	1.020	0.988-1.052	0.224
mPAP	1.025	0.981-1.070	0.275
Glucose	1.006	0.963-1.051	0.795
Creatinine	0.326	0.004-24.581	0.611
eGFR	1.007	0.963-1.054	0.747
NT-pro BNP	1.002	0.999-1.004	0.172
HGB	1.063	0.856-1.320	0.579
HCT	1.031	0.960-1.107	0.399
NLR	1.257	0.704-2.244	0.440
CRP	1.001	0.999-1.002	0.322
HRV	1.010	0.975-1.047	0.567
NIM-index	1.009	0.985-1.033	0.467

LVEF: left ventricular ejection fraction; sPAP: systolic pulmonary artery pressure; mPAP: mean pulmonary artery pressure; HRV: heart rate variability; NIM-index: the neuroimmunomodulation index.

DISCUSSION

Many clinical risk assessment tools researched in patients with PAH. WHO-Functional class, 6-minutes walking distance (6MWD, m) and BNP or NT-pro BNP values are the most valuable and suggested routinely for each patient on clinical follow-up (2). Of these, the WHO-FC is one of the strongest predictors of survival, whether newly or previously diagnosed (6). As expected, NT-pro BNP values were significantly different between the groups in our study.

ECG abnormalities may be useful for the diagnosis of PAH. ECG changes, mostly right axis deviation, combined with other non-invasive tools (e.g. NT-pro BNP) can be used to rule out of PAH diagnosis (7). Bonderman et al. (8) reported a method with 100% sensitivity to exclude pre-capillary PH by combination of ECG and NT-pro BNP on top of ECHO findings. Henkens et al. (9) showed that the combined use of ECG parameters in PAH patients is useful in detecting chronic RV overload. In this study, RV loading was determined by cardiac MRI. Although ECG parameters can be used to rule out or rule in PAH, ECG-based prognostic assessment remains unclear.

CRP, as an inflammatory marker, is associated with poor outcomes in PAH (10). CRP elevation is among the predictors of worse outcomes, including mortality, in adult CHD-related PAH (11,12). Surprisingly, we were not detecting any difference in terms of CRP levels.

HRV is a predictor of worse outcome in children with PAH (13). Yi et al. (14) showed that decreased HRV is associated with PAP and ventricular arrhythmia in patients with idiopathic PAH. Naturally, the need to evaluate the relationship between HRV and PAH treatment arose. Can et al. (15) seek for an answer to exactly this question. As a result, no change was found in HRV with PAH treatment in this study. However, the authors suggest that there is a need for better therapeutic options. In line with the mentioned study, Yoshida et al. (16) designed a preclinical study. They found that electrical vagal nerve stimulation decreased mPAP and improved the survival rate in rats. Although Holter ECG recordings are the preferred method for calculating HRV in the aforementioned studies, short ECG recordings can also be used to calculate HRV (17,18). Hence, we used the standard 12-lead ECGs to calculate HRV.

The parasympathetic system is seeming in closing relationship with inflammatory processes. Previous studies showed that the existence of an "cholinergic anti-inflammatory pathway" and HRV can be used to monitor this activity (19,20). In a recent study, a strong inverse relationship between HRV and CRP was revealed (21).

As a novel indicator, the NIM-index was developed. The first study of the NIM-index was performed on the pancreatic cancer and lung cancer patients (5). In conclusion, authors declared that NIM-index, as a novel marker, associated with prognosis in two fatal cancers. Jarczok et al. (3) tested this index in the general population for overall survival rates. They showed that a lower NIM-index is associated with all-cause mortality in the general population.

There are some limitations to our study. Firstly, this study had a retrospective design and relatively small sample size. Furthermore, this is a single-center study and PAH is a rare disease. Therefore, the sample size in our study can be explained by these. Second, HRV was calculated from short-term ECGs records. Most of the study patients did not have Holter ECG records. Third, this study was planned before the publication of the most recent ESC guideline with a newly changed definition of pulmonary hypertension. Therefore, the mPAP limit in RHC was taken as 25 mmHg for a certain diagnosis. This may also have contributed to the small sample size. Fourth, due to the retrospective study design, 6MWD and WHO-FC data of the patients could not be accessed. Finally, survival analysis could not be performed because the whole study population was alive due of short follow-up period. In lieu of, study patients were compared in terms of hospitalization need.

CONCLUSION

As a result, NIM-index values were not associated with hospitalization in PAH patients. Multicenter, large-scale and long-term studies with Holter ECG monitorization should be designed to display this relevance.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Ankara City Hospital No:1 Clinical Researches Ethics Committee (Date: 07/09/2022, Decision No: E1-22-2807).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients**.**

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